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Neurobiology of Posttraumatic Stress Disorder

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In the general population, posttraumatic stress disorder (PTSD) has a 1% lifetime prevalence (Helzer et al. 1987). Estimates among veterans of war are much higher, with 15% of Vietnam theater veterans currently meeting criteria for PTSD, and 30% meeting lifetime criteria. Since their tour in Vietnam, another 20% of veterans have suffered from partial PTSD, having at least some symptoms disruptive of normal social functioning (Kulka et al. 1990).

The criteria for PTSD include exposure to a stressor beyond the range of normal human experience, with subsequent symptoms of reexperiencing, avoidance, and hyperarousal. Traumatic stressors include a wide range of experiences, such as natural disasters, violent crimes, accidents, and war. When PTSD lasts for longer than 6 months, it is classified as chronic and is often accompanied by symptoms of anxiety, depression, and compromised work and social functioning.

In this chapter, we primarily focus on psychopharmacologic treatment and neurobiological consequences of severe psychological trauma. We review both preclinical and clinical studies relevant to the proposition that PTSD appears to be associated with a significant disturbance of multiple neurobiological systems. At the conclusion of the chapter, an attempt will be made to synthesize much of the data to put forth a more comprehensive theory of the pathophysiology of PTSD. In addition, potential therapeutic implications are discussed.

PSYCHOPHARMACOLOGICAL TREATMENT

Until recently, there have been surprisingly few reports of somatic treatments for the suspected neurobiological symptoms of PTSD. During World War II, amobarbital sodium and thiopental sodium were used in the treatment of acute "combat exhaustion" and "war neurosis" (Kolb 1985) largely for purposes of abreaction and sedation. Another more extreme treatment designed to decrease sympathetic nervous system activation involved bilateral denervation of adrenal glands in war veterans with "neurocirculatory asthenia" (Crile 1940; Krystal et al. 1989). More recently, clinicians and researchers have employed a wide variety of psychopharmacologic agents to treat the acute and chronic symptoms of traumatic stress. However, none of these agents have been successful in treating the full spectrum of symptoms associated with PTSD. Rather, most reports note the improvement of particular symptom clusters within the DSM-III-R (American Psychiatric Association 1987) diagnosis of PTSD or within frequently occurring adjunctive symptom clusters, such as depression or explosive impulsivity.

The most commonly investigated psychopharmacologic agents have been the antidepressants. Antidepressants are a logical treatment choice because of the high

frequency of depressive and panic symptoms in patients with PTSD. The efficacy of antidepressants in the treatment of major depression and panic disorder is well established. Thus far the literature contains four case reports (Hogben and Cornfield 1981; Levenson et al. 1982; Shen and Park 1983; Walker 1982), seven open trials (Birkheimer et al. 1985; Bleich et al. 1986; Davidson et al. 1987; Falcon et al. 1985; Kauffman et al. 1987; Lerer et al. 1987; Milanes et al. 1984), and four double-blind, placebo-controlled trials (Davidson et al. 1990b; Kosten et al. 1991; Reist et al. 1989; Shestatzky et al. 1988) using antidepressants for PTSD. One open trial has addressed acute PTSD; the others have studied chronic PTSD. Subjects in most studies have been combat veterans (Davidson et al. 1990a).

To date, studies of antidepressant use in PTSD have primarily focused on the monoamine oxidase inhibitors and tricyclic antidepressants. Initially there was considerable excitement about the efficacy of phenelzine for PTSD due to a very encouraging case report by Hogben and Cornfield (1981). The authors reported on five combat veterans with traumatic war neurosis. Although these patients had previously failed treatment trials of psychotherapy, antipsychotics, and tricyclic antidepressants, each of the subjects showed a dramatic response to phenelzine, with a marked decrease in nightmares, flashbacks, startle reactions, and aggressive violent outbursts. The authors described phenelzine as possibly "curative." However, subsequent reports of phenelzine have been less enthusiastic. Although phenelzine was found to be of significant overall benefit in an open trial by Davidson et al. (1987) and in a double-blind, placebo-controlled trial by Kosten et al. (1991), phenelzine was found to have minimal treatment efficacy in an open trial by Lerer et al. (1987) and in a placebo-controlled trial by Shestatzky et al. (1988) (Davidson et al. 1990a).

In general, most tricyclic antidepressant treatment trials in PTSD have reported moderate global improvement. For example, the two placebo-controlled trials by Davidson et al. (1990b) and Kosten et al. (1991) found tricyclics to be superior to placebo. The best studied tricyclics have been imipramine and amitriptyline.

Although studies of antidepressant use in PTSD have differed with respect to methodological issues, such as assessment, dosage, and length of treatment, most reports have noted significant improvement in the reexperiencing symptom cluster. In a quantitative review that pooled data from all published antidepressant treatment trials in PTSD, both phenelzine and imipramine were found to be effective for the treatment of reexperiencing symptoms, but not for avoidance, hyperarousal, depressive, or panic symptoms (Southwick et al., in press). The finding that depressive and panic symptoms did not respond to antidepressants needs further clarification since most of the studies did not thoroughly assess for the presence of DSM-III (American Psychiatric Association 1980) or DSM-III-R major depressive disorder or panic disorder.

Other medications that have been used to treat PTSD also appear to decrease some symptoms, but not others (Friedman 1988). For example, autonomic reactivity reportedly diminishes with both clonidine and propranolol; impulsivity and explosiveness respond to both of these agents, as well as to lithium, carbamazepine, and neuroleptics. Although neuroleptics are at times used to treat severe impulsivity, such use is controversial. Lithium may be especially useful for mood lability. Benzodiazepines, among the most frequently prescribed medications for PTSD, appear most effective for anxiety-related symptoms, rather than the core symptoms of PTSD per se. Their use may be limited by their abuse potential and by the tendency for acute withdrawal to increase PTSD-specific symptoms. Finally, avoidance symptoms appear to be

resistant to all psychopharmacologic interventions, with the possible exception of fluoxetine and amitriptyline (Davidson et al. 1990b; McDougle et al. 1991).

PTSD AS A MULTISYSTEM DISORDER

The fact that various symptoms and symptom clusters in patients with PTSD respond to different psychopharmacologic agents with separate modes of action suggests that PTSD, from a neurobiological perspective, may represent a multisystem disorder. For example, if PTSD was caused purely by dysregulation of the noradrenergic system, clonidine would be expected to treat successfully the syndrome as a whole. However, as noted earlier, clonidine is believed to be only partially helpful for a limited number of PTSD symptoms. Similarly, if PTSD was related purely to excessive dopamine function, one might expect neuroleptics to treat the syndrome more successfully. Likewise, fluoxetine would be the only treatment needed if PTSD was solely related to a deficiency in 5-hydroxytryptamine (5-HT) neuronal activity.

A review of the preclinical and clinical neurobiological stress literature relevant to PTSD supports the notion that multiple neurochemical systems are markedly altered in animals and humans who have undergone traumatic stress. Of the enormous number of published preclinical stress studies, this review focuses on those related to the neurochemical and behavioral effects of uncontrollable stress. Uncontrollable stress (where the animal lacks control over stress presentation, intensity, and duration) is a useful animal model of PTSD because the behavioral sequelae so closely resemble symptoms seen in humans with PTSD. Furthermore, stressors that result in PTSD are generally uncontrollable in nature. Our review of the relevant clinical neurobiological literature reports primarily on veterans of war, because the vast majority of investigations have studied this population.

BEHAVIORAL EFFECTS OF UNCONTROLLABLE STRESS

When laboratory animals are exposed to aversive events that are out of their control, such as electric shock, loud noise, or submersion in cold water, they experience profound disturbances in behavior. Initially, there is an alarm response, which is followed by deficits in learning, reduced exploratory behavior, abnormal sleep patterns, and somatic dysfunction, including reduced feeding, weight loss, suppressed immunologic function, increased gastric ulceration, and analgesia (Anisman 1984).

Both the inability to control and the inability to predict the stressor appear to be critical variables in the development of these behavioral and somatic responses (Maier et al. 1986; Tsuda et al. 1989). Although the underlying molecular mechanisms by which uncontrollable stress exerts such profound behavioral effects are currently not known, recent studies in learning and memory suggest that long-term potentiation and behavioral sensitization may be important.

Long-Term Potentiation

Brief, but intense, electrical stimulation of an afferent pathway can lead to long-term potentiation, which is a long-lasting increase in synaptic responsivity to subsequent electrical stimulation. Because of its long-term course, hippocampal locus, and correlation with behavioral learning, long-term potentiation has been proposed as a putative mechanism involved in learning and memory (Teyler and DiScenna 1987).

In animals exposed to uncontrollable stress, several investigators have found that hippocampal long-term potentiation memory and behavioral learning are impaired (Shors et al. 1989). When control is introduced, partial reversal of the impairment may result. The above findings have led some to hypothesize that uncontrollable stress causes impairment in hippocampal long-term potentiation, which then results in long-standing deficits in memory and behavioral learning.

Evidence for long-term potentiation has been found not only in the hippocampus but also in the lateral and basolateral nucleus of the amygdala (Clugnet and LeDoux 1990). Experiments pairing an acoustic stimulus with a foot shock (Chapman et al. 1990) have shown that projections from the medial geniculate body to the amygdala may mediate the formation of traumatic memories. It also has been suggested that emotional memories established via thalamoamygdala pathways may be relatively indelible (LeDoux et al. 1989). These findings raise the possibility that dysfunctional amygdala long-term potentiation may be related not only to the learning abnormalities associated with uncontrollable stress, but also the encoding, storage, and retrieval of traumatic memories.

Behavioral Sensitization

After exposure to uncontrollable threatening or noxious stimuli, animals may exhibit increased behavioral responses to a wide variety of stimuli, both threatening and nonthreatening. The development of sensitization may be strongly related to the memories imprinted by the original stress and by the hormonal and neurochemical brain systems activated by the traumatic experience (Antelman 1988). It has been suggested that the memory traces themselves are associated with a form of sensitization (Squire 1986) and that the intensity of a particular traumatic memory may result from the degree to which key neurochemical systems have been activated by the trauma (McGaugh 1989). Stress-induced sensitization may also partly account for the increased startle response seen in PTSD (Davis 1986, 1989; Hitchcock et al. 1989). Both dopamine and norepinephrine systems have been implicated in the behavioral sensitization that occurs following repeated stress (Kalivas et al. 1990; Nisenbaum et al. 1991).

NEUROCHEMICAL EFFECTS OF UNCONTROLLABLE STRESS AND THE SPECTRUM OF PTSD SYMPTOMS

Profound alterations in multiple neurotransmitter systems are caused by uncontrollable stress. In both the preclinical and clinical literature, the neurochemical systems that have been most studied include noradrenergic, dopaminergic, endogenous opiate, gamma-aminobutyric acid (GABA) benzodiazepine, serotonergic, and hypothalamic-pituitary-adrenal (HPA) axis systems (Tables 18–1 and 18–2).

Noradrenergic Neuronal Function

Uncontrollable stress is associated with an elevated sense of fear and anxiety. In the brain, fear and anxiety may be mediated, in part, by increased activity of the locus coeruleus, resulting in increased synaptic norepinephrine in limbic and cortical regions innervated by the locus coeruleus. Although many types of stressful stimuli produce marked regional (e.g., hypothalamus, hippocampus, amygdala) increases in brain noradrenergic function, uncontrollable stress appears to cause greater increases than controllable stress (Gavin 1985). In fact, when animals have mastered a

Table 18–1. Preclinical evidence for neurobiological dysfunction in posttraumatic stress disorder

Neurochemical system	Functional alteration produced by uncontrollable stress	Acute adaptive behavioral responses
Noradrenergic	Increased regional norepinephrine turnover in limbic and cortical areas Increased responsiveness of locus coeruleus neurons	Anxiety, fear, autonomic hyperarousal, "fight" or "flight" readiness, encoding of traumatic memories, facilitation of sensory-motor responses
Dopaminergic	Increased dopamine release in frontal cortex and nucleus accumbens Activation of mesocortical dopamine neurons	Hypervigilance
Opiate	Increased endogenous opiate release in periaqueductal gray Decreased density of mu opiate receptors in cerebral cortex	Analgesia, emotional blunting, encoding of traumatic memories
Benzodiazepine	Decreased density of benzodiazepine receptors in hippocampus and cerebral cortex Reduced GABA-dependent chloride flux	Fear, hyperarousal
Hypothalamic-pituitary-adrenal axis	Elevated glucocorticoid levels at the level of the hippocampus	Metabolic activation, learned behavioral responses

Note. GABA = gamma-aminobutyric acid.

Table 18–2. Clinical evidence for neurobiological dysfunction in posttraumatic stress disorder

Neurobiological dysfunction	Evidence	Potential clinical correlates	Reference
Autonomic reactivity	↑ resting heart rate ↑ resting systolic blood pressure ↑ heart rate in response to visual and auditory reminders of trauma	Hyperresponsivity to stress, increased cardiovascular morbidity	Orr 1990
Adrenergic and noradrenergic function	↑ 24-hour urinary epinephrine and norepinephrine	Chronic anxiety, fear, impulsivity, anger	Kosten et al. 1987
	↑ plasma epinephrine in response to combat-related stressful stimuli	Persistent hypervigilance	McFall et al. 1990
	↓ platelet alpha$_2$-adrenergic receptor number	Reactivation of traumatic memories	Perry et al. 1987
	↑ internalization of platelet alpha$_2$-adrenergic receptors in response to in vitro agonist stimulation	Chronic hyperarousal	Perry et al. 1990
	↑ behavioral and MHPG responses to yohimbine		Southwick et al. 1991

Hypothalamic-pituitary-adrenal axis function	↑↓ 24-hour urinary cortisol	Possible difficulties in learning and memory	Pitman and Orr 1990; Yehuda et al. 1990
	↑ lymphocyte glucocorticoid receptor number		Yehuda et al. 1991a
	↓ ACTH response to CRH		Smith et al. 1989
	↑ sensitivity to dexamethasone		Yehuda et al. 1991b
Endogenous opiate function	↑ stress-induced analgesia reversed by naloxone	Chronic "numbing" and blunting of emotional responses	Pitman et al. 1990; van der Kolk et al. 1989

Note. ↑ = increased. ↓ = decreased. MHPG = 3-methoxy-4-hydroxyphenylglycol. ACTH = adrenocorticotropic hormone. CRH = corticotropin-releasing hormone.

coping task to reduce stress effectively, increased norepinephrine turnover generally does not occur (Tsuda and Tanaka 1985).

A number of investigations have shown that uncontrollable but not controllable stress produces increased responsivity of locus coeruleus neurons to excitatory stimulation. This locus coeruleus hyperactivity may result from the development of alpha$_2$-adrenergic autoreceptor subsensitivity (Simson and Weiss 1988a, 1988b). In addition, stress-induced increase in norepinephrine turnover is associated with a decrease in postsynaptic beta-receptor number (Torda et al. 1984).

Sensitization and noradrenergic function. Altered noradrenergic function may be associated with behavioral sensitization to repeated stress. When animals are exposed to repeated stressors, tyrosine hydroxylase, dopamine beta-hydroxylase activity, and synaptic levels of norepinephrine metabolites increase (Irwin et al. 1986b; Kramarcy et al. 1984; Melia et al. 1991). These findings suggest that repetitive stress can cause a compensatory increase in the synthesis of norepinephrine. Thus when repeatedly shocked animals are reexposed to limited shock, they respond with a degree of norepinephrine release that is more appropriate for much greater degrees of shock.

Environmental stimuli previously paired with uncontrollable shock may also lead to sensitization or fear conditioning of noradrenergic neuronal systems. Neutral stimuli that have been paired with inescapable shock produce increases in brain norepinephrine metabolism and behavioral deficits similar to that elicited by the original shock (Cassens et al. 1981). Neurophysiologic studies in freely moving cats indicate that pairing a neutral stimulus with an aversive one, which increases locus coeruleus firing, results in the neutral stimulus acquiring the same property (Rasmussen et al. 1986).

Clinical studies. For years, investigators have speculated about the relationship between symptoms of severe stress and the sympathetic nervous system in traumatized humans. Meakins and Wilson (1918) found shell-shocked veterans to have greater increases in heart rate and respiratory rate than healthy controls when exposed to sulfuric flames and the sounds of gunfire. Exaggerated psychophysiologic arousal responses were noted in war veterans when they were administered intravenous epinephrine (Fraser and Wilson 1918). Since the 1980s, there have been a series of well-designed psychophysiologic studies that have consistently documented heightened sympathetic nervous system arousal in combat veterans with PTSD (Orr 1990). Compared with healthy controls, veterans with PTSD tend to have a higher mean resting heart rate and systolic blood pressure, and they tend to show greater increases in heart rate when exposed to visual and auditory combat-related stimuli in the laboratory. This same degree of hyperreactivity has not been found in combat veterans without PTSD or in combat veterans with anxiety disorders other than PTSD. Taken together, the psychophysiologic studies suggest that some individuals are more susceptible to sympathetic nervous system dysregulation than others and that neither combat alone nor the presence of anxiety disorders other than PTSD is sufficient to explain postwar physiologic hyperreactivity. Additionally, it has been shown that not all stressful stimuli evoke hyperreactive responses in traumatized combat veterans; hyperreactive responses seem relatively specific to combat-related stressful stimuli, suggesting that noradrenergic reactivity in patients with PTSD may be conditioned or sensitized to specific traumatic stimuli (Orr 1990).

Investigations of neuroendocrine and peripheral catecholamine receptor systems have also provided evidence for a dysregulation of sympathetic nervous system activity in PTSD. Kosten et al. (1987) found that 24-hour urine norepinephrine excretion was higher in combat veterans with PTSD than in patients with schizophrenia or major depression. Further, throughout the course of hospitalization, norepinephrine excretion in the PTSD group remained markedly elevated in comparison to values reported for other subjects. In a study of alpha$_2$-adrenergic receptors, Perry et al. (1987) found 40% fewer receptors in a group of patients with PTSD compared with non-psychiatrically-ill control subjects. A decreased receptor number most likely reflects adaptive "down-regulation" in response to chronically elevated levels of circulating endogenous catecholamines. In addition, using an in vitro model of intact platelets, high concentrations of epinephrine caused a more rapid and extensive loss of receptor protein from the platelet membrane, probably due to a more rapid internalization process (Perry et al. 1990).

In the first study to evaluate simultaneously psychophysiologic reactivity and peripheral catecholamines in combat veterans with PTSD, McFall et al. (1990) found a parallel rise in blood pressure, heart rate, subjective distress, and plasma epinephrine during and after a combat film, suggesting that elevations of circulating catecholamines are related to hyperreactive physiologic responses. In residents living within 5 miles of the Three Mile Island nuclear power plant, south of Harrisburg, Pennsylvania, similar elevations in resting heart rate, blood pressure, and urinary norepinephrine have been reported (Davidson and Baum 1990).

Although most studies of neurobiological function in PTSD have employed peripheral measures of catecholamine metabolism, preliminary evidence for central catecholamine dysregulation comes from a recent investigation using intravenous yohimbine as a probe of central and peripheral noradrenergic function. Although yohimbine affects multiple neurotransmitter systems, in panic disorder it has been proposed that yohimbine induces panic attacks by increasing noradrenergic function through a blockade of alpha$_2$-adrenergic receptors (Charney et al. 1987). As predicted from preclinical studies, intravenous yohimbine induced enhanced behavioral, biochemical, and cardiovascular responses in combat veterans with PTSD compared with non-psychiatrically-ill control subjects (Southwick et al. 1991). Approximately 60% of patients with PTSD had yohimbine-induced panic attacks; approximately 40% had flashbacks. In contrast, yohimbine rarely induces panic attacks in patients with schizophrenia, major depression, obsessive-compulsive disorder, or generalized anxiety disorder or in healthy control subjects (Charney et al. 1990a). However, the 60% rate of yohimbine-induced panic attacks closely resembles the rate seen in patients with pure panic disorder (Charney et al. 1987), suggesting that PTSD and panic disorder share a common neurobiological abnormality related to the noradrenergic system. Comorbid panic disorder could not solely account for panic attacks in PTSD since panic attacks were experienced by patients both with and without comorbid panic disorder.

Uncontrollable Stress and Dopaminergic Neuronal Function

The prefrontal cortex is the primary brain dopamine system involved in the stress response. Biochemical and electrophysiologic studies have shown that stress preferentially activates and increases the firing rate of mesocortical neurons compared with mesolimbic and strata dopamine areas (Dunn 1988; Roth et al. 1988). Increases in dopamine metabolism in the frontal cortex also have been noted in association with

environmental cues that have been paired with a stressor (Herman et al. 1982). A number of chemically distinct afferent systems seem to play a role in stress-induced activation of mesocortical dopamine, including substance P, *N*-methyl-D-aspartate (NMDA), and opiates (Dunn 1988).

Chronic stress and repeated cocaine exposure may have similar effects on dopamine neuronal function. Both appear to increase mesocortical dopamine transmission in response to acute stress. Further, locomotor responses to cocaine and amphetamine increase after daily exposure to stress (Antelman et al. 1980; Kalivas and Duffy 1989; Maclennan and Maier 1983; Robinson et al. 1985).

Clinical studies. Because enhanced dopamine function has been related to psychosis in schizophrenia, it is possible that symptoms of stress-induced psychosis are also related to dopamine neuronal hyperactivity. Trauma-related psychosis in Nazi concentration camp survivors, Vietnam veterans, and Cambodian refugees has been described in case reports and small descriptive studies (Kinzie and Boehnlein 1989; Mueser and Butler 1987; Nemeth 1960). These reports are difficult to interpret due to the possibility that these individuals may have developed psychotic disorders in the absence of trauma, and due to the complexity of distinguishing dissociative and psychotic symptoms. Hypervigilance and paranoia have also been reported in traumatized individuals. In fact, these symptoms are frequently seen in combat veterans with PTSD.

Uncontrollable Stress and Endogenous Opiate System Function

Uncontrollable stress stimulates a release of endogenous opiates, causing substantial and significant hypoalgesia (Hemingway and Reigle 1987). Further, in rats previously exposed to uncontrollable shock, reexposure with less intense shock reproduces the same degree of hypoalgesia, suggesting that sensitization occurs. This hypoalgesia is likely to be mediated by stress-induced release of endogenous opiates because opiate peptides are elevated after acute uncontrolled shock (Maier 1986). Uncontrollable, but not controllable, shock decreases the density of mu opiate receptors, and stress-induced analgesia is blocked by naltrexone (Stuckey et al. 1989).

The actual induction of behavioral deficits resulting from uncontrollable stress may also, in part, be mediated by endogenous opiates. Hippocampal long-term potentiation and behavioral deficits do not develop when naltrexone is given prior to uncontrollable shock (Hemingway and Reigle 1987).

Clinical studies. Naloxone has been shown to reverse stress-induced analgesia in both nontraumatized and traumatized human populations. After noxious foot shock (Hemingway and Reigle 1987) and during uncontrollable problem-solving tasks (Bandura et al. 1988) in nontraumatized humans, stress-induced analgesia can be reversed by naloxone. Similarly, naloxone reverses the analgesia induced by stressful combat films in Vietnam veterans with PTSD (Pitman et al. 1990). These findings suggest that stress-induced analgesia in PTSD is, at least in part, opiate mediated. The findings are consistent with the observation that soldiers in World War II required lower doses of narcotics than did civilians with less severe injuries (Beecher 1946).

It has been hypothesized that compulsive reexposure to traumatic events or "addiction to trauma" is related to increases in endogenous opiates during episodes of reexposure to the trauma or reminders of the trauma (van der Kolk et al. 1989). However, psychophysiologic laboratory studies have failed to support this hypoth-

esis; combat films in veterans with PTSD evoked numbing or blunting of emotional responses, as opposed to euphoria or emotional feelings of calm and control (Pitman et al. 1990). This association between psychic numbing and opiate-mediated stress-induced analgesia is supported by studies of self-mutilation in traumatized psychiatric patients (Richardson and Zaleski 1983).

Uncontrollable Stress and Benzodiazepine Receptor Function

Decreases in GABA receptor–mediated chloride ion flux, depolarization-induced hippocampal release of GABA, and brain benzodiazepine receptor occupancy have all been associated with behavioral deficits induced by uncontrollable shock (Drugan et al. 1989). Uncontrollable stress causes a decrease in benzodiazepine receptor binding in cerebral cortex, hippocampus, and striatum, and a reduction of the density of low-affinity $GABA_A$ receptors and chloride efflux and uptake in cerebral cortex (Concas et al. 1988a; Drugan et al. 1989; Schwartz et al. 1987). Additionally, foot shock stress and anxiogenic beta-carbolines increase [^{35}S]TBPS (t-butylbicyclophosphomethionate) binding in rat cerebral cortex (Concas et al. 1988b). These findings suggest that the behavioral effects of uncontrollable stress are associated with a functional alteration of the benzodiazepine GABA chloride ionophore complex.

Lorazepam and chlordiazepoxide, both benzodiazepines, prevent the development of the behavioral deficits and analgesia induced by uncontrollable stress (Drugan et al. 1984). The benzodiazepine receptor inverse agonist beta-carboline FG-7142 (*N*-methyl-β-carboline-3-carboxamide), on the other hand, produces behavioral deficits very similar to those seen in uncontrollable shock. Pretreatment with a benzodiazepine receptor antagonist, Ro 15-788, prevents the effects of FG-7142 (Drugan et al. 1985).

The effects of uncontrollable stress in the benzodiazepine system may in part be related to alterations in norepinephrine, dopamine, and endogenous steroid systems. For example, benzodiazepines reduce locus coeruleus activity, as well as stress-induced increases in norepinephrine turnover (Ida et al. 1985; Redmond 1987). Benzodiazepines also decrease stress-induced increases in prefrontal dopamine activity. Additionally, it is now known that several endogenous steroids are potent modulators of the $GABA_A$ benzodiazepine chloride ionophore receptor complex (Majewska et al. 1986).

Clinical studies. Although there have been no specific studies to date relating the symptoms of PTSD to dysfunction of the benzodiazepine GABA system, there is extensive preclinical and accumulating clinical evidence implicating the benzodiazepine GABA receptor in the pathophysiology of human anxiety and general fear states. For example, FG-7142, a benzodiazepine receptor inverse agonist, causes severe anxiety and panic attacks in healthy subjects (Dorow et al. 1983). Similarly, flumazenil, a benzodiazepine receptor antagonist, induces panic attacks in some patients with panic disorder, but not in healthy subjects, suggesting that the sensitivity of benzodiazepine receptors to inverse agonists may be increased (Nutt et al. 1990; Woods et al. 1991). The use of benzodiazepine inverse agonists and antagonists in patients with PTSD and the measurement of behavioral and cerebral metabolic effects of these drugs using positron-emission tomography (PET) and single photon emission computed tomography (SPECT) imaging techniques will provide for a better understanding of the role of the benzodiazepine GABA system in symptom formation.

Uncontrollable Stress and Serotonergic Neuronal Function

Inescapable shock, but not escapable shock, decreases serotonin levels in the lateral septum and cortex (Petty and Sherman 1983). On the other hand, immobilization stress increases brain 5-HT turnover and 5-hydroxyindoleacetic acid (5-HIAA) concentrations (Keneth and Joseph 1981). Supporting the finding that inescapable shock reduces serotonin levels is the fact that serotonin antagonists (methysergide and parachlorophenylalanine [PCPA]) can cause behavioral effects that resemble those seen in inescapable shock (Morgan et al. 1975). Additionally, when serotonin agonists (parachloroamphetamine [PCA], 5-HT_{1A} agonists) are administered before inescapable shock, the subsequent behavior deficits can be prevented (Giral et al. 1988).

Establishing the precise role of serotonin in the behavioral effects of uncontrollable stress is complicated by the fact that noradrenergic and serotonergic neuronal systems interact with and regulate one another in the brain. For example, 5-HT_2 binding sites are elevated in rat cortex as a result of acute stress and immobilization. However, this effect is dependent on the integrity of the brain noradrenergic system and not the 5-HT system (Torda et al. 1990). Clearly, further preclinical investigations will be needed to delineate the precise role of the serotonin system in uncontrollable stress.

Clinical studies. The role of serotonin function in human forms of anxiety, fear, and stress is not well understood. m-Chlorophenylpiperazine (mCPP), a partial serotonin agonist with complex interactions at the 5-HT receptor, has been shown to have anxiogenic properties in healthy subjects and in patients with panic disorder, supporting a role for serotonergic neurons in the pathophysiology of anxiety (Charney et al. 1990b; Soubrie 1986). Although the precise 5-HT receptor type most affected by mCPP is not fully delineated, recent evidence suggests an important role for the 5-HT_{1c} receptor (Seibyl et al. 1991). The effects of mCPP in patients with PTSD are currently being investigated.

Serotonin may play an important role in the regulation of mood, aggression, impulsivity, and compulsive behavior. These affects and behaviors are commonly seen in traumatized individuals, suggesting that dysfunction of serotonergic neurons may play a role in symptom formation in PTSD. The use of fluoxetine for the treatment of a variety of symptoms of PTSD is currently under investigation. Preliminary data appear encouraging, with possible efficacy for avoidance symptoms as well as reexperiencing symptoms (McDougle et al. 1991).

Uncontrollable Stress and HPA Axis Function

In laboratory animals, adrenocorticotropic hormone (ACTH) and cortisol levels are increased by acute stress of many types (McEwen et al. 1986). It has been shown that high glucocorticoid levels decrease hippocampal but not other brain glucocorticoid receptors, resulting in increased corticosterone secretion and feedback resistance. With uncontrollable stress, but not controllable stress, this feedback resistance results in nonsuppression of cortisol in response to dexamethasone. With the resolution of acute stress, glucocorticoid levels again decrease, receptor number increases, and feedback sensitivity normalizes (Sapolsky and Plotsky 1990).

Both adaptation and sensitization of glucocorticoid activity have been reported in response to chronic stress. Some investigators have reported that adaptation to chronic stress may occur, with resultant decreases in plasma ACTH and cortisol levels (Kant et al. 1985). Other investigators have reported an increased cortisol secretion

following chronic stress as well as augmented cortisol responses to a subsequent stressor, particularly in animals with prior histories of stress (Irwin et al. 1986a).

It is unclear exactly how the effects of uncontrollable stress on the HPA axis affect behavior. There is some evidence to suggest that elevated glucocorticoid levels may result in learning deficits through neurotoxic effects on hippocampal neurons. In a study of vervet monkeys, marked and preferential hippocampal degeneration was noted in deceased animals after sustained social stress (Uno et al. 1989). In a second investigation with vervet monkeys, glucocorticoid administration resulted in very similar damage to the hippocampus (Sapolsky et al. 1990). Other evidence for a relationship between uncontrollable stress, alteration in the HPA axis, and behavior comes from adrenalectomy experiments. In general, adrenalectomy and resultant decreased corticosteroid levels increase the frequency of behavioral and learning deficits caused by uncontrollable stress. These deficits may be reversed by corticosteroid administration (Edwards et al. 1990). It appears, then, that a certain amount of glucocorticoid activity is necessary for learning and adaptation but that too much activity may result in neurotoxicity.

Just as serotonergic and noradrenergic systems appear to have regulatory effects on one another in the brain, so glucocorticoids and biogenic amines appear to have modulating effects on one another (McEwen 1987). For example, norepinephrine stimulates corticotropin-releasing hormone (CRH) secretion from the hypothalamus (Calogero et al. 1988); stress-induced glucocorticoid elevation may mediate the ability of stress to reduce norepinephrine-stimulated cyclic AMP in the hippocampus and cortex. Because CRH and corticosterone (Avanzino et al. 1987; Valentino et al. 1983) each activate locus coeruleus neurons, it is possible that under conditions of stress the CRH systems and noradrenergic systems mutually reinforce one another.

Clinical studies. Under conditions of acute stress, both norepinephrine and cortisol secretion increase. Norepinephrine prepares the organism for action; cortisol generally serves a metabolic preservation function. In studying chronic stress, however, Mason et al. (1988) found low cortisol levels in the presence of elevated norepinephrine, suggesting a dissociation between the pituitary-adrenal-cortical axis and the sympathetic-adrenal-medullary system. This unusual discordance between norepinephrine and cortisol has been used as a means to discriminate chronic combat-related PTSD from other psychiatric diagnoses.

The data on urinary cortisol in chronically stressed combat veterans have been conflicting. One group reported an increased level (Pitman and Orr 1990); a second group found unusually low cortisol levels in comparison with healthy control subjects and subjects with other psychiatric diagnoses (Yehuda et al. 1990). Earlier work with animals suggested that the underlying mechanism of low cortisol is not one of pituitary-adrenal-cortical system exhaustion, but rather most likely involves a central suppressive or inhibitory mechanism (Yehuda et al. 1991c).

Consistent with these data, combat veterans with PTSD have been found to have a greater number of lymphocyte glucocorticoid receptors compared with healthy control subjects (Yehuda et al. 1991a). In a variety of tissues, glucocorticoids appear to play a role in the regulation of glucocorticoid receptor number, with decreased cortisol levels resulting in a compensatory increase in number of receptors and increased cortisol levels in a decreased number of receptors.

Also consistent with low cortisol levels is the finding that some patients with PTSD may be overly sensitive to the ability of dexamethasone to suppress cortisol (Yehuda

et al. 1991b). That is, the HPA axis, most likely at the level of the hypothalamus or pituitary, may hyperrespond to dexamethasone. The resultant heightened negative feedback could be the result of an increased number or sensitivity of hypothalamic-pituitary glucocorticoid receptors. Heightened negative feedback to glucocorticoids might also explain Smith et al.'s (1989) finding of a blunted ACTH response to CRF in patients without abnormally high circulating cortisol levels.

COMMENT

Acute Neurobiological Responses to Severe Trauma

Under conditions of acute and severe psychological trauma, the organism mobilizes multiple neurobiological systems for the purpose of survival. Thus noradrenergic, benzodiazepine, opiate, dopaminergic, serotonergic, and HPA axis systems may all be activated simultaneously. These systems appear to interact functionally with one another as the organism attempts to cope with impending danger. In addition to the simultaneous functional alteration of different neurochemical systems during acute stress, several brain structures, most notably the amygdala, hippocampus, locus coeruleus, and prefrontal cortex, also appear to become activated. For example, activation of the locus coeruleus produces an increase in norepinephrine release at locus coeruleus projection sites, including the amygdala, hippocampus, and cerebral cortex. As reviewed above, these structures are markedly affected by uncontrollable stress, are functionally and neuroanatomically interrelated, and may mediate many of the symptoms of PTSD.

The simultaneous alterations of numerous brain neurochemical systems and structures during acute traumatic stress likely represent adaptive responses critical for survival. Endogenous norepinephrine, benzodiazepine, and dopamine appear to mediate fear, autonomic hyperarousal, and hypervigilance, each of which facilitates appropriate behavioral reactions to threat. Norepinephrine additionally appears to influence numerous somatic functions, including blood pressure, heart rate, and blood clotting. The metabolic activation necessary for sustained physical demands and tissue repair appears to be influenced by trauma-induced cortisol hypersecretion. Secretion of endogenous opiates reduces pain sensitivity of men wounded in battle, which may be critical for survival. Finally, the encoding of traumatic memories that will facilitate appropriate response to future danger may be facilitated by norepinephrine and opiate systems.

Chronic Neurobiological Sequelae

Although initially beneficial, neurobiological responses to trauma may have long-term negative consequences that are related to many of the chronic symptoms of PTSD. For example, the dysregulation of noradrenergic neurons may result in a system that is persistently hyperresponsive to stress, particularly stress that is in some way related to the original trauma. Symptoms of chronic hyperarousal and anxiety may result. Preclinical studies demonstrating stress-induced alpha$_2$-autoreceptor dysfunction and stressor desensitization of noradrenergic neurons support this notion.

Noradrenergic system hyperactivity may also be related to the reexperiencing symptoms of PTSD. During the original trauma, when encoding of memories takes place, the individual is in a state of heightened noradrenergic activity. It is quite

possible that this physiologic state of hyperarousal becomes associated with the original trauma, and now by itself has the capacity to evoke traumatic memories and flashbacks. It is well known that traumatic memories can be reactivated decades after the original trauma by stressful life events completely unrelated to the original stressor. Preclinical studies invite the speculation that traumatic memories can be evoked by stress-induced activation of the locus coeruleus with increased norepinephrine release and stimulation of noradrenergic receptors in brain regions such as the amygdala and hippocampus. Recent clinical studies with yohimbine support this notion.

Patients with chronic PTSD frequently exhibit increased anger, hostility, impulsivity, and dysphoria. These symptoms may be related to abnormalities in either norepinephrine, 5-HT, or both. Further experience with selective norepinephrine and selective 5-HT pharmacologic agents should clarify the relationship between specific neurotransmitter systems and particular symptoms of PTSD. Another potentially important long-term consequence of the acute response to trauma involves persistent difficulties in learning and memory, possibly due to glucocorticoid-induced hippocampal damage.

The high rates of substance abuse in combat veterans with PTSD may also be related to the noradrenergic system. Alcohol, opiates, and benzodiazepines are commonly considered the preferred substances of abuse among traumatized combat veterans. Each of these drugs decreases the firing rate of the locus coeruleus and decreases norepinephrine release and turnover in various brain loci. The use of these drugs by traumatized veterans might then represent an attempt to compensate for dysregulation of catecholamine or endogenous opiate systems. On the other hand, amphetamines and cocaine, which increase dopamine function, may actually increase symptoms of hyperarousal and paranoia.

Implications for Therapeutics of PTSD

PTSD can be a devastating disorder with a wide array of symptoms, including the core clusters of reexperiencing, avoidance, and hyperarousal, as well as adjunctive symptoms such as paranoia, anger, impulsivity, compulsivity, depression, and panic attacks. As a disorder, PTSD can be chronic in nature and difficult to treat. Until recently, the disorder largely has been understood from a psychological, social, and behavioral standpoint. Psychosocial treatments in PTSD rely on 1) abreaction, 2) desensitization, 3) insight, 4) cognitive restructuring, and 5) social support (Beck 1976; Bernstein and Borkovec 1973; Bowen and Lambert 1986; Brende and Parson 1985; Brown and Fromm 1986; Catherall 1986; Crasilneck and Hall 1985; Figley 1985; Flannery 1987; Freud 1914; Horowitz 1986; Johnson 1987; Lindy 1986; Lyons and Keane 1989; Shatan 1973). Of these approaches, only abreactive and desensitization techniques attempt to eliminate the source of ongoing PTSD symptoms. The others focus on reducing the ill effects of trauma and increasing the individual's capacity to cope with the condition. Collectively, these psychosocial treatments have brought much relief to victims of trauma. Unfortunately, however, they have had limited effectiveness in fully treating the core symptoms of PTSD. As suggested by the above review, many of the core symptoms may reflect underlying neurobiological disturbances and, as such, are more likely to respond to treatments specifically targeted at these disturbances.

To improve treatment response in patients with PTSD, many more carefully designed cognitive, physiological, behavioral, and neurobiological studies are

needed. Neurotransmitter and neuropeptide functions must be comprehensively assessed shortly after and at intervals following different types of severe stress. The spectrum of stress-induced clinical symptoms also needs to be related to the function of identified neurochemical systems and brain regions. Important tools for investigating some of these relationships include magnetic resonance imaging, PET, and SPECT. Family and genetic studies will also be important for determining premorbid vulnerability.

With a better understanding of the psychobiology of traumatic stress, it may be possible to develop more effective and specific treatment approaches for PTSD. At present, because no one therapeutic modality has emerged as the treatment of choice, patients seem to benefit most from a combination of therapies. For example, although antidepressants may be effective for reexperiencing symptoms, concurrent behavioral therapy or traditional psychodynamic psychotherapy can be used to manage other symptoms, such as avoidance and guilt. Even after more is known about the pathophysiology of PTSD, because so many neurochemical systems are involved, it seems unlikely that any one pharmacologic agent will be sufficient to treat the entire spectrum of symptoms seen in PTSD.

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